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# Primary prophylaxis with letermovir for prevention of CMV infection in two children

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## Cytomegalovirus

Cytomegalovirus (CMV), a human herpesvirus HHV5, is present in latent form in 40%–70% children and 60%–90% of adults [1]. In patients after allogeneic hematopoietic cell transplantation (allo-HCT), it can reactivate either as recipient or donor origin. The virus can cause direct and indirect toxicity [2, 3]. Direct effects can cause organ infections (enteritis, pneumonia, hepatitis, bone marrow suppression, and retinitis) and toxicity, while indirect effects refer to associated adverse effects of antiviral therapy and increased risk of bacterial and fungal infections, and further suppression of immune system. Additionally, CMV seropositive status of recipient and/or donor, CMV reactivation, and CMV infection/disease cause decreased survival after hematopoietic cell transplantation (HCT) [4, 5, 6]. According to current knowledge, guidelines, and clinical experience, the best preventive strategy for CMV infection after allo-HCT in the year 2020 is specific antiviral prophylaxis with letermovir [7, 8, 9]. This drug is currently registered worldwide for primary prophylaxis for CMV-seropositive adults after allo-HCT. The objective of this clinical vignette is presentation of safe and efficacious use of letermovir for primary prophylaxis of CMV infection in two children after allo-HCT.

## Patient 1

A 15-year-old girl, with body weight 58 kg, diagnosed for severe aplastic anemia (SAA), after failure of immunoablative therapy with anti-thymocyte globulin (ATG) + steroids + granulocyte colony stimulating factor (GCSF) + romiplostim, was qualified for HCT. Due to lack of sibling or matched unrelated donor, a haploidentical mother was selected to be the donor. Conditioning (fludarabine (FLU) + cyclophosphamide (CY) + single dose total body irradiation (sTBI) + ATG) and prophylaxis of graft-versus-host disease (GVHD) [post-transplant cyclophosphamide (PTCy) + cyclosporin A (CsA) + mycophenolate mofetil (MMF)] was performed according to Bacigalupo regimen [10]. No acute GVHD occurred. Due to CMV seropositivity of donor and recipient, the patient was administered prophylactically letermovir, orally from day 1. The dosage was 240 mg daily, and the patient was on CsA. The drug was well tolerated and no adverse effects were reported. No toxicities of ciclosporin A were observed and the CsA levels were stable. Due to pneumonia and respiratory insufficiency, the patient died without T-cell engraftment on day 60. Polymerase chain reaction (PCR) DNA-emia CMV on day 60 was negative (Fig. 1).

## Patient 2

A 7-year-old boy, with body weight 27 kg, diagnosed for T-cell acute lymphoblastic leukemia (ALL), was qualified for HCT due to lack of remission by day 33 preceded by initial poor steroid response and presence of minimal residual disease. He was transplanted from female matched unrelated donor. Conditioning (total body irradiation (TBI) + etoposide) and prophylaxis of GVHD (PTCy + CsA + MMF) was performed. No acute GVHD occurred. Due to CMV seropositivity of donor and recipient, the patient was administered prophylactically letermovir, orally from day 1. The dosage was 120 mg daily, and the

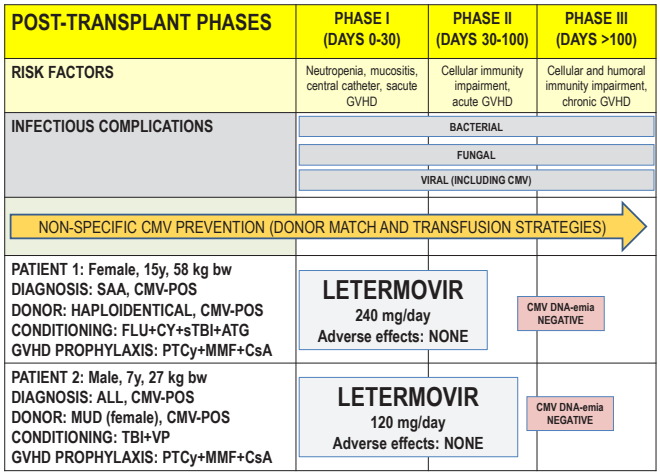


***Fig 1. Use of letermovir for primary prophylaxis of CMV infection in two children***

*GVHD – graft-versus-host disease; SAA – severe aplastic anemia, CMV-POS - cytomegalovirus-positive; FLU+CY+sTBI+ATG – fludarabine + cyclophosphamideand +single dose total body irradiation + anti-thymocyte globulin; PTCy+MMF+CsA – post-transplant cyclophosphamide + mycophenolate mofetil + cyclosporin A; MUD – matched unrelated donor; ALL – T-cell acute lymphoblastic leukemia,*

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patient was on cyclosporine A. The drug was well tolerated and no adverse effects were reported. No toxicities of CsA were observed and the CsA levels were stable. T-cell engraftment (CD4+ >200/µl) was reached by day 60, and letermovir was discontinued by day 80, PCR DNA-emia CMV on day 90 was negative (Fig. 1).

## Discussion

Due to its extremely favorable safety profile, letermovir brings potential for the use in clinical situations, other than approved indication. We decided to administer letermovir to our two patients being at very high risk of CMV reactivation. In Patient 1, we applied typical dosing as for adults when concomitantly treated with cyclosporine A. As the patient body weight was 58 kg, it was comparable to adults. With pediatric approach, the drug was administered at dosage of 4.1 mg/kg bw. In Patient 2, with body weight 27 kg, we decided to use letermovir at the daily dose of 120 mg, which corresponded to pediatric dosing 4.4 mg/kg bw. In summary, in both cases the administration of letermovir was safe and protected the patients from CMV reactivation, as confirmed in several PCR assays.

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### *Authors' contributions*

JS – was responsible for the study design and provided administrative support. KC, JS – carried out data analysis and interpretation and manuscript writing. All the authors – carried out data check-up and provided final approval.

### *Conflict of interest*

JS has received scientific grants or served at the speakers' bureau of MSD. All other authors declared no conflict of interest related to this study.

### *Financial support*

None.

### *Ethics*

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; uniform requirements for manuscripts submitted to biomedical journals.

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